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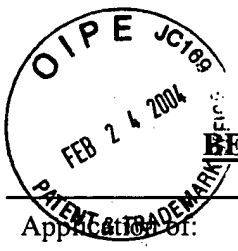

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Rittershaus & Thomas
Serial No.:	09/943,334
Filed:	August 30, 2001
Entitled:	MODULATION OF CHOLESTERYL ESTER TRANSFER PROTEIN (CETP) ACTIVITY

ON APPEAL

Examiner: 1644

Art Unit: M. Belyavskyi

Attorney Docket No.: TCS-411.1P US-1

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF and PETITION FOR EXTENSION OF TIME

Sir:

Transmitted herewith: [X] a Brief on Appeal, with Appendices A-D, in triplicate; [X] a check (no. 5054) in the amount of $1170.00 in payment of the fees under 37 C.F.R. § 1.17(a)(5)and 37 C.F.R. § 1.17(c); and [X] a return-receipt postcard, for filing in the above-captioned patent application. The following checked items are also appropriate:

[X] Small entity status has been established previously for Applicants in this case.

PAYMENT OF ADDITIONAL FEES

[X] A check including the amount of **$ 165.00** in payment of the fees for filing a brief in support of an appeal is transmitted herewith. {check no. 5054}

[X] The Commissioner is hereby authorized to charge payment of any additional fees required under 37 CFR 1.16 or 1.17 in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No. 50-0268. A duplicate copy of this transmittal letter is transmitted herewith.

PETITION FOR EXTENSION OF TIME

[X] Extension is requested under 37 CFR 1.136(a), and the following extension fee is applicable for the Response filed herewith: [ ] $55.00 for response within first month pursuant to 37 CFR 1.17(a)(1);
[ ] $210.00 for response within second month pursuant to 37 CFR 1.17(a)(2);
[ ] $475.00 for response within third month pursuant to 37 CFR 1.17(a)(3);
[ ] $740.00 for response within fourth month pursuant to 37 CFR 1.17(a)(4);
[X] $1005.00 for response within fifth month pursuant to 37 CFR 1.17(a)(5).

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[X] A check including the amount of [ ] $55.00 [ ] $210.00 [ ] $475.00 [ ] $740.00 **[X] $1005.00** in payment of the extension fee is transmitted herewith. {check no. 5054}

[X] The Commissioner is hereby authorized to charge payment of any additional fees required in connection with the paper(s) transmitted herewith, or to credit any overpayment of same, to Deposit Account No. 50-0268. A duplicate of this transmittal letter is submitted herewith.

Respectfully submitted,

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Stephanie L. Leicht

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
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Group Art Unit: 1644

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Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Sir:

Pursuant to 37 C.F.R. §1.192, Appellants submit this Brief on Appeal in triplicate, setting forth the basis of their appeal from the Office Action, mailed April 22, 2003 (Paper No. 8) finally rejecting Claims 28, 29, and 37-39 of the above-identified patent application.

Notice of Appeal pursuant to 37 C.F.R. §1.191 was timely filed on July 24, 2003.

This Brief is accompanied by the filing fee under 37 C.F.R. §1.17(c) and a petition for extension of time and fee under 37 C.F.R. §1.17(a)(5). The Commissioner is authorized to charge any additional fees required in connection with the filing of this Brief to PTO Deposit Account No. 50-0268.

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REAL PARTY IN INTEREST

Appellants hereby identify AVANT IMMUNOTHERAPEUTICS, INC., formerly T CELL SCIENCES, INC., a corporation organized and existing under the laws of the State of Delaware and having an office and place of business in Needham, Massachusetts, as the assignee of the invention disclosed in the present application.

RELATED APPEALS AND INTERFERENCES

This appeal is directly related to appeals filed in Ser. No. 08/432,483, decided December 18, 2001 in Appellant's favor, and in Ser. No. 08/945,289, prosecution reopened before Examiner's Answer withdrawing substantive rejections. The present application is a division of Ser. No. 08/945,289, now U.S. 6,555,113 (attached at Tab C), which is a continuation-in-part of Ser. No. 08/432,483, now U.S. 6,410,022 (attached at Tab B).

There are no related interferences.

STATUS OF CLAIMS

The present divisional application was filed on August 30, 2001 with original Claims 1-36. A Preliminary Amendment cancelling Claims 1-27 and 30-36, and adding new Claims 37, 38, and 39, was filed concurrently with the application papers.

The Examiner issued an election of species requirement (Paper No. 4) on April 8, 2002, requiring Appellants to elect a species of universal helper T cell epitope from the group recited in dependent Claim 29 for examination. Appellants traversed the election requirement in a Response submitted May 8, 2002 but provisionally elected tetanus toxoid as the universal T cell epitope portion for prosecution, with all claims readable thereon.

In the first Office Action on the merits (Paper No. 6), dated July 30, 2002, the Examiner rejected Claims 28, 29, and 37-39 under 35 U.S.C. §112, first and second paragraph. In addition, the Examiner rejected Claims 28-29, and 37-39 under 35 U.S.C. §103 based on a combination of four references, and rejected Claim 39 under 35 U.S.C. §103 based on a combination of six references.

In a Response submitted January 30, 2003, Appellants amended Claims 28, 29, and 37 and filed a terminal disclaimer with regard to the predecessor application Ser. No. 08/432,483 (now U.S. 6,410,022).

A final rejection was mailed April 22, 2003.

Appellants filed Notice of Appeal on July 24, 2003, without requesting further amendment of the claims.

The appealed Claims 28, 29, and 37-39 appear in the attached Appendix (Tab A). A copy of U.S. 6,410,022, with claims directed to vaccine peptides, methods of use, and methods of treatment related to the appealed claims is attached at Tab B. A copy of U.S. 6,555,113, with claims directed to methods of use related to the appealed claims is attached at Tab C.

STATUS OF AMENDMENTS

All of Appellants' amendments have been entered.

SUMMARY OF INVENTION

Atherosclerosis is a disease characterized by the accumulation, over time, of fatty deposits, or plaque, in the lumen of blood vessels. Accumulation of plaque eventually leads to partial or total occlusion of the vessels, which may lead to more serious manifestations of cardiovascular disease, such as myocardial infarct. (*See*, e.g., The Dictionary of Cell and Molecular Biology, Lackie & Dow, eds. (Academic Press, London 1999), definition of *atherosclerosis* at pp. 41-42, copy attached at Tab D.)

Decreased susceptibility to atherosclerosis and related cardiovascular disease is inversely correlated with increased absolute levels of circulating high density lipoprotein (HDL) and also increased levels of HDL relative to circulating levels of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) (*see*, e.g., Appellants' specification at p. 2, lines 10-16; p. 24, lines 15-19).

Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl ester from HDL to triglyceride-rich lipoproteins such as VLDL and LDL, and also the reciprocal exchange of triglycerides from VLDL to HDL (*see*, e.g., specification at p. 2,

lines 17-23). High CETP activity has been correlated with decreased levels of HDL-associated cholesterol and with increased levels of LDL-associated cholesterol and VLDL-associated cholesterol, which increased levels in turn are correlated with increased risk of cardiovascular disease (specification at p. 2, lines 23-26; p. 3, line 29-p. 4, line 1; p. 24, lines 11-19).

Data supporting a causal relationship between CETP activity, relative HDL level, and progression of atherosclerosis is presented by Appellants' specification (*see*, Example 6 (p. 32), Example 9 (p. 37), Example 10 (p. 38)).

Human CETP is an abundant, circulating glycoprotein of 476 amino acids having the ability to bind cholesterol ester (CE), triglycerides, phospholipids, and lipoproteins (*see*, e.g., specification at p. 3, lines 11-16).

Appellants' invention relates to the concept of modulating or inhibiting the activity of circulating CETP in order to control the relative levels of lipoproteins and to possibly decrease or prevent the development of atherosclerosis (*see*, specification at p. 5, lines 28-32; p. 7, line 30-p. 8, line 4; p. 24, lines 11-19). Appellants' novel approach, however, is not to directly regulate CETP activity by injection of inhibitory substances. Rather, Appellants' invention provides methods and compositions for actively immunizing a subject against its endogenous CETP for the treatment or prevention of atherosclerosis in the subject. In other words, Appellants propose to induce antibody recognition, by a subject's own immune system, of its own, endogenous (or "self") CETP. Such immune recognition of self has been demonstrated by Appellants to result in modulation and inhibition of CETP activity with beneficial effects (*see*, Examples 4, 5, 6, 7, 9, and 10 of Appellants' specification). The use of this immunization approach for treatment or prevention of atherosclerosis is the subject of the appealed claims (*see*, Appendix attached at Tab A).

In particular, the claimed methods of the invention comprise administering to a human or animal an antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein the B cell epitope portion comprises a B cell epitope of CETP (*see*, specification, e.g., at p. 5, lines 1-9; p. 12, line 28-p. 16, line 21). Thus, the methods of the invention induce production of antibodies

(i.e., autoantibodies) in an individual, which antibodies specifically target and inhibit the individual's endogenous CETP, leading to the results of beneficial lipoprotein profiles (such as an elevated level of HDL relative to LDL, VLDL, or total cholesterol) decreased or prevented development of atherosclerotic lesions.

An example of a conjugate peptide comprising a B cell epitope linked to a T cell epitope useful in the methods of the invention is the conjugate peptide having the amino acid sequence of SEQ ID NO:2, which has an amino terminal cysteine residue linked to a 14 amino acid peptide of tetanus toxoid, which in turn is linked to a 16 amino acid peptide from the carboxy-terminal region of human CETP. A conjugate peptide having a tetanus toxoid as a universal helper T cell epitope portion is the elected species of the conjugate peptide used by the Examiner to examine the methods of appealed Claims 28, 29, and 37-39. Administration of peptide conjugates, such as those having the amino acid sequence of SEQ ID NO:2, according to Appellants' methods has surprisingly led to favorable changes in the circulating levels of HDL and total cholesterol as demonstrated in statistically significant experimental results (*see*, e.g., Example 4, p. 31 and Fig. 6; Example 9, p. 37 and Fig. 12) and, even more surprising, has been demonstrated to actually reduce accumulation of atherosclerotic plaque in vaccinated animal subjects as compared with subjects not receiving the treatment of the present invention (*see*, Example 10, p. 38, and Fig. 13).

SUMMARY OF THE REFERENCES CITED BY THE EXAMINER

The following references are relied on (in combination) as the basis for the rejections maintained by the Examiner:

1. Whitlock et al., *J. Clin. Invest.*, 84: 129-37 (1989) [hereinafter "Whitlock"];
2. Stevens et al., U.S. 6,143,305 [hereinafter "Stevens"];
3. Swenson et al., *J. Biol. Chem.*, 264(24): 14318-26 (1989) [hereinafter "Swenson"];
4. Valmori et al., *J. Immunol.*, 149: 717-21 (1992) [hereinafter "Valmori"];

5. Talwar et al., *Proc. Natl. Acad. Sci. USA, 91*: 8532-36 (August 1994) [hereinafter "Talwar"]*; and
6. Stanton et al., U.S. 5,807,552 [hereinafter "Stanton"]*.

Whitlock

The Whitlock document describes a short term passive immunization study of CETP activity wherein a murine monoclonal antibody reactive with human CETP is administered to rabbits to study *in vivo* inhibition of CETP activity. Administration of the anti-huCETP antibody was shown to inhibit CETP activity in rabbits by about 70% immediately after infusion, which inhibition fell to about 44% after 48 hours (*see*, e.g., Fig. 2, p. 131 of Whitlock). Appellants specifically note that the Whitlock experiments employ an infusion of pre-made, murine anti-human CETP monoclonal antibody into a rabbit (i.e., passive immunization). There is no teaching or suggestion in Whitlock of actively immunizing an individual against their own CETP.

Stevens

Stevens describes the design and use of a vaccine against establishing pregnancy by attempting to raise antibodies against endogenous chorionic gonadotropin. Example XXXI shows a vaccine construct consisting of a 37-mer peptide from the β subunit of human chorionic gonadotropin (β-hCG) covalently linked to tetanus toxoid. This human peptide/tetanus toxoid construct was administered to baboons to alter menstrual cycle. Stevens describes various other methods, such as haptenization, of modifying hormones and administering the modified hormones to inhibit hormone activity.

Appellants note that hCG and the other hormones mentioned in Stevens are completely unrelated to CETP, and regulating fertility by immunization (described by Stevens) is completely different from treating or preventing atherosclerosis (claimed herein). Stevens does not teach or suggest active immunization against a constitutively produced endogenous protein, and does not teach or suggest immunization against a protein involved in cholesterol metabolism. Stevens does not teach or suggest active

* Appellants do not concede that these references are prior art (see discussion *infra*).

immunization against a protein as large as CETP (~70kD). Stevens does not teach or suggest active immunization against a protein as abundant in circulation as CETP. Stevens does not teach or suggest active immunization to affect circulating cholesterol metabolism or to treat coronary artery disease. And Stevens does not teach or suggest the concept of actively immunizing an individual against their own CETP or any other protein involved in lipid metabolism.

Swenson

Swenson describes the isolation of a murine monoclonal antibody, designated TP2, that binds to an epitope contained within the carboxy-terminal 26 amino acids of human CETP. Comparative binding assays performed with TP2 indicated that complexing of TP2 with CETP interfered with the neutral lipid binding activity of CETP.

There is no mention in Swenson of the concept of active immunization of an individual to continuously control CETP activity via an endogenous immune response.

Valmori

Valmori describes synthetic multimeric *Plasmodium* antigen constructs which are tested for their ability to raise an antibody response to plasmodium sporozoites and which might therefore be useful as a vaccine protective against malaria. The synthetic constructs of Valmori employ multiple copies of tandem repeat sequences from the circumsporozoite protein from one of two different *Plasmodium* species (i.e., -Asn-Ala-Asn-Pro- or -Asp-Pro-Pro-Pro-Pro-Asn-Pro-Asn), which are made into non-linear tetramers or octamers by attachment to a polylysine core of a multiple antigen peptide (MAP) system (*see*, e.g., p. 717, right column, and Table II of Valmori).

The experiments reported by Valmori showed that the multimer antigen constructs raised polyclonal antibodies that recognized natural *Plasmodium* circumsporozoite protein; however, a linear antigen of 40 Asn-Ala-Asn-Pro repeats did not raise an antibody response. *See*, Table II, p. 718, of Valmori.

Some Valmori constructs also employed one or two tetanus toxoid antigens ("P2" or "P30", at p. 717, Materials and Methods of Valmori), and inclusion of either or both of the tetanus antigens increased antibody response.

Valmori is concerned with vaccines against malaria, a disease caused by a non-endogenous parasite. There is no mention in Valmori of the concept of actively immunizing an individual against any endogenous protein. There is no suggestion in Valmori of immunizing an individual against their own CETP.

Talwar

Talwar describes the design and use of a vaccine against establishing pregnancy. The successful vaccine of Talwar contains a heterospecific, multimeric protein antigen consisting of the β subunit of human chorionic gonadotropin (β-hCG) noncovalently linked to sheep (ovine) luteinizing hormone (LH), conjugated to tetanus or diphtheria toxoid, and mixed with a sodium phthalyl derivative of lipopolysaccharide for primary immunization against the endogenously and pulsatorily produced hCG hormone in order to prevent the development of pregnancy. Talwar also describes the failure of a simplified vaccine against pregnancy in which β-hCG was linked to tetanus toxoid (*see*, second paragraph on p. 8532 of Talwar). Thus, Talwar describes an unpredictable method of regulating (i.e., inhibiting) the native hormone hCG, which is completely unrelated to CETP, using a complex, heterospecies, multimeric complex vaccine, in order to prevent a condition (pregnancy) which is completely distinct from cardiovascular disease.

Talwar does not teach or suggest active immunization against a constitutively produced protein. Talwar does not teach or suggest active immunization against a large protein. Talwar does not teach or suggest active immunization against an abundant protein. Talwar does not teach or suggest active immunization to affect circulating cholesterol metabolism or to treat coronary artery disease. And Talwar does not teach or suggest the concept of actively immunizing an individual against their own CETP or any other protein involved in lipid metabolism.

In addition, Appellants discovered that Talwar cannot be properly relied on by the Examiner as a reference for examination of this application under 35 U.S.C. §103. The instant application is a division of Ser. No. 08/945,289 (now U.S. 6,555,113), which is a continuation-in-part of Ser. No. 08/432,483 (now U.S. 6,410,022) filed May 1, 1995, which is less than one year from the August 1994 publication date of Talwar. To remove Talwar from consideration, Appellants submitted a Declaration Under 37 C.F.R. §1.131 by co-inventors Charles W. Rittershaus and Lawrence J. Thomas with their Amendment after final rejection on April 14, 2000 in the parent to the present application mentioned above. The Rule 131 declaration shows that conception of the claimed invention occurred prior to the August 1994 publication date of Talwar and was followed by diligent work to reduce the present invention to practice. In particular, the Rule 131 declaration clearly establishes Appellants' priority of at least as much of the claimed invention as the reference Talwar happens to show, as required by law. *See, In re Stempel*, 241 F.2d 755, 113 USPQ 77 (CCPA 1957). Accordingly, not only does Talwar fail to provide any teaching or suggestion of Appellants' claimed methods or any teaching or suggestion relevant to Appellants' methods, it does not even qualify as a prior art reference for the purposes of examining the claims of this application.

In the parent case, the Examiner refused to accept the Rule 131 declaration as persuasive to eliminate Talwar, and Appellants petitioned the Commissioner for reconsideration of the Rule 131 declaration and withdrawal of Talwar as a reference (Petition submitted July 27, 2000). Subsequently, Talwar was removed from consideration in the parent case. For the sake of completeness, Appellants will discuss Talwar along with other references relied on by the Examiner or otherwise made of record. However, notwithstanding any other statements that mention or may refer to Talwar in this Brief, Appellants do not admit that Talwar is prior art to this invention.

Stanton

Stanton describes the design of vaccines against human immunodeficiency virus (HIV) based on the HP-6 epitope, the T cell epitope of HIV. Stanton is relied on for its teaching relating to multimerization of peptide immunogens using interlinking peptides.

Appellants point out that Stanton does not mention active immunization against a constitutively produced self protein; Stanton relates only to the design of vaccines against a viral pathogen. Stanton does not teach or suggest active immunization to affect circulating cholesterol metabolism or to treat coronary artery disease. And Stanton does not teach or suggest the concept of actively immunizing an individual against their own CETP or any other protein involved in lipid metabolism.

Furthermore, Appellants point out that the Stanton reference is not prior art to Appellants' disclosure: The Stanton patent issued in 1998 on an application filed August 4, 1995, which is a date occurring after the May 1, 1995 filing date Appellants claim the benefit of under 35 U.S.C. §120/121.

ISSUES ON APPEAL

The issues for consideration in the present appeal are:

I. Whether the substance of the final rejections (paper no. 8) has already been presented and decided in Appellants' favor in the parent and grandparent applications from which the present application is descended and to which the present application claims the benefit under 35 U.S.C. §§120 and 121.

II. Whether Appellants' specification, acknowledged to be enabling for methods of treating atherosclerosis using a CETP vaccine peptide comprised of SEQ ID NO: 2 or a dimer thereof, or a vaccine peptide comprised of a helper T cell epitope linked to a B cell epitope comprising between 6 and 26 amino acids of the carboxy-terminal 26 amino acids of human CETP (SEQ ID NO: 1), is nevertheless non-enabling for a method of preventing atherosclerosis.

III. Whether Appellants' specification, acknowledged to demonstrate Appellants' possession of methods of treating atherosclerosis using a CETP vaccine peptide comprised of SEQ ID NO: 2 or a dimer thereof, or a vaccine peptide comprised of a helper T cell epitope linked to a B cell epitope comprising between 6 and 26 amino acids of the carboxy-terminal 26 amino acids of human CETP (SEQ ID NO: 1), is nevertheless insufficient to provide a written description of a method

for preventing atherosclerosis by using the same CETP vaccine peptides or vaccines comprising any B cell epitope of CETP.

IV. A. Whether the methods recited in appealed Claims 28, 29, 37 and 38 would, at the time of Appellants' invention, have been obvious to a person of ordinary skill in the art of immunology in view of the combined teachings of: Whitlock in view of "the known fact disclosed in [Appellants'] specification on page 2, lines 10-12", Stevens, Swenson, and Valmori.

B. Whether the method recited in appealed Claim 39 would, at the time of Appellants' invention, have been obvious to a person of ordinary skill in the art of immunology in view of the combined teachings of: Whitlock in view of "the known fact disclosed in [Appellants'] specification on page 2, lines 10-12", Stevens, Swenson, and Valmori, further in view of Talwar or Stanton.

GROUPING OF THE CLAIMS

With respect to the grounds of rejection under 35 U.S.C. §112, first paragraph, relating to enablement, the appealed claims present definitions of varying scope, therefore Claims 28, 29, 37 and 38 must be considered separately. Claims 38 and 39 stand or fall together with respect to issues of enablement.

With respect to the grounds of rejection under 35 U.S.C. §112, first paragraph, relating to written description, each of the appealed claims defines different embodiments described in different parts of the specification. Therefore, Claims 28, 29, 37, 38, and 39 must be considered independently in light of the specification to determine the sufficiency of the written description to communicate that Appellants were in possession of the particular claimed embodiment at the time of filing.

With respect to the rejection of Claims 28, 29, 37 and 38 under 35 U.S.C. §103(a), Appellants believe that appealed Claims 28, 29, 37 and 38 stand or fall together. (Claim 39 is rejected separately under 35 U.S.C. §103(a) and stands by itself.)

ARGUMENTS

The final rejection of the appealed claims is in error for the following reasons:

1. The issues of enablement, written description and obviousness over the prior art presented by the Examiner in the final Office Action have already been addressed and resolved (in Appellants' favor) by this Board or other Examiners in the parent and grandparent applications to the present application, resulting in U.S. Patent Nos. 6,410,022 and 6,555,113 (*see* Tabs B and C). Therefore, the final rejection re-raises questions of law already settled in Appellants' favor, and this appeal is unnecessary and wasteful. However, in order to be completely responsive, Appellants will address the final rejections as if they were issues presented to the Board *de novo*.

2. The data presented in Appellants' specification are directly applicable to and enabling for methods for prevention of atherosclerosis, i.e., by showing that the methods of the appealed claims, practiced on test mammals, led to reduced accumulation of atherosclerotic plaque in treated animals in comparison to control animals not receiving such treatment. Moreover, guided by the express teachings of Appellants' specification, particularly Section 1.B., entitled "B Cell Epitope (CETP-Related) Portion of Vaccine Peptides," at pages 12-16 of the specification and Figs. 8A and 8B, and in view of the working examples provided, it is within the skill of practitioners in this art to select a suitable B cell epitope portion from any region of a CETP, link that portion to a universal helper T cell epitope, and administer the hybrid peptide to a mammalian subject to treat or prevent atherosclerosis. It is also within the skill in the art thereafter to determine whether the administration has led to an immune response characterized by proliferation of antibodies that bind the subject's endogenous CETP and alter *in vivo* CETP activity. It follows that the methods of the appealed claims could be readily practiced by persons skilled in this art by following the teachings of the specficiation, without experimentation, to treat or prevent atherosclerosis using the entire range of hybrid CETP vaccine peptides

encompassed by the appealed claims, and thus the enablement requirement of 35 U.S.C. §112, first paragraph, has been fully satisfied.

3. The actual reduction to practice of a method for treating and preventing atherosclerosis set forth in the working examples, and the detailed description of alternative embodiments included in the specification, clearly demonstrates, in accordance with the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, Jan. 5, 2001, pp. 1099-1111, that Appellants were in full possession of their invention as claimed at the time the application was filed.

4. (a) Any combination of the publications cited by the Examiner in rejecting the claims lacks at least one critical factor: There is no indication from any reference that any person in the art has ever conceived of the idea of actively immunizing an individual to modulate the activity of that individual's own CETP *in vivo* for the purpose of treating or preventing atherosclerosis. That idea came from the Appellants only. Thus, there is no substantial evidence of a sufficient motivation or teaching to combine the references relied on by the Examiner to reject Appellants' Claims 28, 29, and 37-39 as obvious within the meaning of 35 U.S.C. §103(a).

(b) Even if the references can be considered properly combined, the combinations of references proposed by the Examiner in rejecting Appellants' claims fail in a second critical factor: There is no demonstration in any prior art publication of any method that successfully treats or prevents atherosclerosis. Appellants, for instance, have shown in controlled experiments that their method results in retarding the deposition of atherosclerotic plaque in the arteries of test mammals. No similar data, demonstration, *or even conjecture* that plaque formation can be directly affected by an immunological treatment appears in any of the references or in any combination of the references.

(c) Taking the record as a whole, there is much more evidence in the prior art of the failure of active immunization to control the activity of an endogenous protein than evidence of success. This being evident from the prior art, including the prior art relied

on by the Examiner, and also considering the pronounced differences between CETP and the only self protein discussed in the citations (i.e., human chorionic gonadotropin, or hCG), it simply cannot be concluded that a person of ordinary skill in the art at the time of Appellants' invention could form a reasonable expectation *from the state of the art* that endogenous CETP activity could be successfully controlled by active immunization *and* that such control would provide an effective therapy for the treatment or prevention of atherosclerosis. For this reason, no *prima facie* case of obviousness is presented by any combination of the cited references.

(d) Even if the references are considered properly combined, and even if a *prima facie* case of obviousness is considered to be made out, neither the magnitude and duration of the immunological response, nor the pronounced effect on atherosclerosis disease progression using the methods of the invention could have been expected or predicted by a person of ordinary skill in the art at the time Appellants' invention was made. Given the sparse immunological data presented in the prior art, such unexpected results obtained by Appellants clearly indicate the unobviousness of the presently claimed methods of treatment.

The following discussion provides the factual and legal basis for the reasons set forth above for finding error in the final rejection of Appellants' claims:

I. The Substance of the Final Rejections Has Been Previously Resolved in Related Ancestor Applications, in Appellants' Favor

The subject matter of the appealed claims, i.e., a method of treating or preventing atherosclerosis, was originally presented in the parent application, Ser. No. 08/945,289, now U.S. 6,555,113 (Tab C). As a result of a restriction requirement, the now-appealed claims were withdrawn in favor of prosecuting claims related to methods for (a) elevating the ratio of HDL to LDL in an individual, (b) decreasing the level of endogenous CETP activity, (c) altering HDL-cholesterol catabolism, and (d) increasing the level of circulating HDL. *See*, Tab C, Claims 1, 6, 8, and 9. The present application was filed to secure consideration of the non-elected claims.

During prosecution of the parent application, the same Whitlock (cited as a primary reference in the present case), Swenson, Valmori, and Talwar references were cited in combination by the examiner in that case to reject the claimed invention as obvious. After filing a Brief on Appeal, prosecution was reopened and the claims to methods of elevating HDL/LDL ratio, etc., were allowed. *See*, claims of U.S. 6,555,113, at Tab C. It is noted that the method claims of the parent application, now U.S. 6,555,113, are not limited as to selection of the CETP B cell epitope (that is, not limited to B cell epitope portions selected from the C-terminal 26 amino acids, as sought by the Examiner in the present application).

In addition, during prosecution of Ser. No. 08/432,483 (now U.S. 6,410,022, Tab B), the grandparent of the present application, the same Whitlock, Swenson, and Valmori references were also combined by the examiner in that case to reject the claims as obvious. This Board reversed the rejections based on Whitlock, Swenson, and Valmori, and this led to the issuance of U.S. 6,410,022 (attached at Tab B). It is of particular moment that Claim 18 of that patent is directed to:

> 18. **A method of treating atherosclerosis** in a human or animal comprising administering to the human or animal an antigenic vaccine hybrid peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises six to 26 consecutive amino acids of the carboxyl terminal 26 amino acids of human cholesteryl ester transfer protein.

Comparison of this claim with the present claims on appeal reveals that the Patent Office has already determined that the subject matter of the appealed claims is patentable, insofar as the antigenic vaccine utilizes a B cell epitope of CETP selected from the C-terminus of the protein, whereas the claims on appeal are broader to the extent of directing that the B cell epitope may be selected from any region of the CETP protein, so long as a vaccine peptide incorporating such B cell epitope effectively elicits the desired autoimmune reaction. Thus, the claims presently on appeal differ from the subject matter of Claim 18 of U.S. 6,410,022 only in terms of scope – incidentally a scope that was approved for method claims in the parent case, U.S. 6,555,113 – and therefore the final rejection of the appealed claims in this case is submitted to be clearly erroneous.

Appellants assert that the Examiner has misinterpreted the individual and combined teachings of the citations as they pertain to the appealed claims in a manner similar to the two previous appeals involving this subject matter, from which Appellants' two patents have issued. Appellants submit that the issues raised by the Examiner with respect to these references have in fact been raised and considered previously by this Board, which decided that these references, either individually or taken together, do not provide any teaching or suggestion of Appellants' vaccine peptides or their use to modulate an individual's native CETP activity.

Appellants submit that the issues presented in this appeal are not issues that are raised *de novo* in connection with the subject matter disclosed in the present application but rather are issues already raised in earlier ancestor applications, to the level of appeal, and which have been resolved in Appellants' favor. Accordingly, as a matter of logic and consistent application of the law, Appellants request reversal of the final rejections.

In order to be fully responsive and to comply with the requirements of 37 C.F.R. §1.192, Appellants will address the substance of the final rejections below.

II. Demonstration and Enablement of Prevention of Atherosclerosis

In the final Office Action of April 22, 2003, the Examiner rejected Claims 28-29 and 37-39 under 35 U.S.C. §112 stating,

> "As was stated in the Previous Office Action . . . the issue is whether or not the claimed method would function for preventing atherosclerosis. The nature of the invention is such that it would require the administration of vaccine peptide to prevent a mammalian subject from having atherosclerosis." (*See*, Office Action, page 3). (emphasis in original).

It is apparent, upon review of Appellants' disclosure, that a demonstration of prevention of atherosclerosis in a mammalian subject is set forth in the working examples. Atherosclerosis is a disease marked by the accumulation of arterial plaque over time (*see*, Tab D). Thus, direct evidence of prevention of the formation of such plaque would be direct evidence of prevention of the disease.

Appellants conclusively show in their application that rabbits that were fed a diet high in cholesterol, i.e., a diet that is known to directly cause the formation and accumulation of aortic plaque, and that received a CETP vaccine peptide in accordance with the claimed methods, had significantly less aortic plaque formation than rabbits that were fed the same atherogenic diet but did not receive the vaccine.

Example 6, beginning on page 32, describes the feeding and vaccination regimen for four test groups. Rabbits of Group I were administered a CETP vaccine peptide and fed a high cholesterol diet; rabbits of Group II were vaccinated and fed a low cholesterol diet; Group III rabbits were not vaccinated and fed a low cholesterol diet; and Group IV (control) rabbits were not vaccinated and fed a high cholesterol diet.

Example 10, beginning on page 38, describes the removal and analysis of aortas from all of the surviving rabbits from Example 6 after 17 weeks. Each aorta was opened and analyzed for formation of atherosclerotic lesions, i.e., development of atherosclerosis.

The dramatic results are shown in Figure 13: Comparison of Group I and Group IV (control) rabbit aortas, shows that Group I (vaccinated/high cholesterol diet) exhibited a statistically significant reduction in the overall occurrence and size of lesions as compared to the extent and size of atherosclerotic lesions in the Group IV animals (no vaccination/high cholesterol diet). Specifically, as disclosed in the application, the results demonstrated that administration of a CETP vaccine peptide according to the present invention was capable of retarding the formation of atherosclerotic lesions in animals fed a high cholesterol diet *by greater than 50%*, thus preventing atherosclerosis in the treated group. Non-vaccinated animals (Group IV) had lesions that covered an average of 45% of the total area of the aorta, whereas vaccinated animals (Group I) had lesions that covered an average of only 19% of the total area of the aorta.

In other words, the data of the present application clearly demonstrate to persons skilled in this art that administration of a vaccine of the present invention actually prevents aortic plaque formation in a widely used mammalian model of atherosclerosis. As such, Appellants are entitled to coverage of this prophylactic aspect of their invention.

With respect to the scope of the present claims the Examiner states,

> "Applicant is relying upon certain biological activities and the disclosure of a limited number of species to support an

> entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated *any* vaccine peptide, comprising universal helper T cell epitope portion linked to and *any* B cell epitope of CETP encompassed by the claimed invention other than antigenic vaccine peptide comprising the amino acid sequence of SEQ ID NO: 2 or a dimer thereof or comprising a universal helper T cell epitope portion linked to B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO: 1 would be expected to have greater differences in their acitivities." (See, final Office Action, page 4). (emphasis in original).

Appellants note that no evidence is presented to support the Examiner's conclusion relating to the expectation of differences in the activities of vaccine peptide embodiments covered by the claims but not specifically exemplified in the specification. In any event, the critical activities for the vaccine peptides are expressly recited in the claims, i.e., regardless of the selected component helper T cell epitope and CETP B cell epitope portions, the vaccine peptide must elicit an antibody response in the subject AND antibodies produced as a result of the administration of the vaccine peptide must also recognize endogenous, circulating cholesteryl ester transfer protein.

Appellants point out that the present claims are drawn to methods of treating atherosclerosis by administering

> ". . . an antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises a B cell epitope of CETP." (Claim 28, emphasis added)

The claim language outlined above clearly sets forth the finite metes and bounds of the present invention and its limitation in scope. An "antigenic vaccine peptide" containing both a "universal helper T cell epitope portion" and "a B cell epitope portion comprising a B cell epitope of CETP" is a structurally defined sequence of amino acids.

Furthermore, as recited in the claims, the hybrid vaccine peptide must be "antigenic" in that it effectively elicits an antibody response corresponding to the B cell epitope portion. These antibodies must in turn recognize and bind the full-length endogenous CETP protein as it exists in the individual receiving the vaccine peptide. In other words, the meaning of "antigenic" is that the vaccine peptide as defined in the claims has the ability to elicit the production of native antibodies (autoantibodies) that are reactive with native CETP. (*See*, definition of "antigenic" at p. 10, lines 10-14, of the specification.)

It is seen that the appealed claims do not recite the use of *any* B cell epitope of CETP, rather the claims recite the use of a vaccine peptide, comprised of at least two structural components (universal helper T cell epitope portion and B cell epitope portion), which vaccine peptide is antigenic (as defined in the specification).

As to selection of the B cell epitope portion, the complete sequence of the human CETP protein is disclosed in the present specification (SEQ ID NO:4), and an entire section of the specification (pp. 12-16) is devoted to describing suitable B cell epitopes of CETP for use in a vaccine peptide according to the invention. All of the information necessary to select B cell epitope candidates, to link them to universal helper T cell epitope portions to form vaccine peptides, and to administer them to humans or animals and detect whether they elicit an autoimmune anti-CETP antibody response is provided by Appellants' specification.

The standard for an enabling disclosure under 35 U.S.C. §112, first paragraph, has been clearly set forth in holdings of the CCPA and its successor court, the CAFC:

> "It has been consistently held that the first paragraph of 35 USC 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)."

The patent law recognizes that an enabling disclosure does not need to describe every possible embodiment covered by the claims:

> "The law does not require the impossible. Hence, it does not require that an applicant describe in his specification every conceivable and possible future embodiment of his invention. The law recognizes that patent specifications are written for those *skilled in the art*, and requires only that the inventor describe the "best mode" known at the time to him

> of making and using the invention. 35 U.S.C. §112" *SRI International v. Matsushita Electric Corporation of America*, 775 F.2d 1107, 1121, 227 USPQ 577 (CAFC 1985) (italics and underlining in original).

An objection to the specification as not providing an enabling disclosure cannot be based on broad statements of a conclusion of non-compliance with §112. On the contrary, to establish a *prima facie* case of non-compliance with 35 U.S.C. §112, first paragraph, there must be **evidence or a reasonable explanation** as to why an applicant's disclosure does not amount to an effective teaching of the invention to a person skilled in the art:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used describing and defining the subject matter sought to be patented **must be taken as in compliance with the enabling requirement** of the first paragraph of §112 **unless there is reason to doubt the objective truth of the statements contained therein** which must be relied on for enabling support.
>
> * * *
>
> "In any event, **it is incumbent upon the Patent Office,** whenever a rejection on this basis is made, **to explain** why it doubts the truth or accuracy of any statement in a supporting disclosure and **to back up** assertions of its own **with acceptable evidence or reasoning which is consistent with the contested statement.**" *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, (Fed. Cir. 1971) (emphasis added).

Appellants respectfully submit that the Examiner has not met this standard. The broad conclusory statements of the rejection fail to provide any evidence or reasoning why a person skilled in this art would not be able to practice the entire scope of Appellants' teaching. Accordingly, Appellants assert that a *prima facie* case for lack of an enabling disclosure under 35 U.S.C. §112, first paragraph, has not been made out; that ample guidance and teaching from the detailed description and working examples has been provided for the skilled artisan to support the entire breadth of the claims; and, finally, that the present claims employ terms and terminology that have already been

found to be fully enabled under U.S. patent law in the parent and grandparent applications.

Again, in the final Office Action, the Examiner improperly focuses on the enablement of specific sequences while ignoring that the specification, in detail, teaches one skilled in the art how to test additional CETP B cell epitope sequences for autoantigenicity.

For example, the specification explicitly describes an actual process for selecting and for testing CETP vaccine peptides to determine whether they elicit an immune response against endogenous CETP:

First, Example 1, beginning on page 27, demonstrates the construction of a peptide for testing,

> "To investigate the possibility of eliciting an antibody response against endogenous CETP, a peptide was prepared having a helper T cell epitope portion comprising a universal tetanus toxoid helper T cell epitope and a B cell epitope portion comprising a carboxyl terminal region of human CETP. A 31-amino acid peptide was designed having the amino acid sequence [omitted] (SEQ ID NO:2), in which Q Y I K A N S K F I G I T E (amino acids 2 to 15 of SEQ ID NO:2) is the same amino acid sequence as amino acids 830 to 843 of the tetanus toxoid protein, F G F P E H L L V D F L Q S L S (amino acids 16 to 31 of SEQ ID NO:2) is the same amino acid sequence as amino acids 461 to 476 . . . of human CETP and known to be recognized by anti-human CETP Mab TP2. . ." (*See*, page 27, lines 15-24).

Next, the specification describes administration of this vaccine peptide to a mammalian subject,

> "The synthetic peptide (SEQ ID NO: 2) of Example 1 above was injected into New Zealand White Rabbits to test the ability of the vaccine peptide to elicit an immune response against endogenous rabbit CETP." (*See*, page 28, lines 4-6).

The specification describes the post-injection steps to determine antigenicity,

> "The general protocol for testing the vaccine peptide in the rabbits is shown in Figure 1 . . . On Day 1, peptide (100μg)

> was suspended to 1000µl . . . and each rabbit . . . was injected at two intramuscular sites (250µl per site) . . . subcutaneously at two sites (100µl per site) . . . and six intradermal sites (50µl per site). On Day 28, a boost . . . On Day 56, another boost . . . Blood samples (approximately 1-5 ml) were withdrawn from the ear of each rabbit prior to each initial injection ("prebleed") and on Days 42 , 70, and 108, . . . Blood plasma samples were prepared by standard centrifugation methods to separate cellular components from the plasma. Plasma samples were stored at -70° C. Plasma samples of both Groups I and II were analyzed for presence of and increase in titer of anti-CETP antibodies and for total plasma cholesterol and plasma HDL-C levels. (*See*, page 28, lines 9-23).

Next the specification describes testing the blood samples for presence of anti-CETP antibodies,

> "A sandwich enzyme-linked immunosorbent assay (ELISA) was used to titer plasma samples containing anti-CETP antibody. In this set-up, recombinant human CETP . . . was adsorbed to wells of a microtiter dish, and various dilution of rabbit plasma from the rabbits . . . were added to each well . . . In this assay, the O.D. was directly proportional to the amount of anti-CETP antibodies present in the plasma samples. The results indicated that all of the rabbits . . . produced anti-CETP antibody which was specific for recombinant human CETP." (*See*, page 28, line 24, to page 29, line 21).

In the foregoing manner, the antigenicity of a vaccine peptide according to the present invention may be determined. In Examples 6-10, beginning at page 32, line 25, of the specification, it is demonstrated how such an antigenic vaccine peptide was able to retard the development of atherosclerosis in a mammalian model.

The Examiner has not explained or offered evidence as to why a person skilled in the art of immunology could not follow the procedures exemplified with any other B cell epitope candidate derived from a CETP. Nor is there any explanation or evidence as to why a person skilled in the art, who reads the entire specification and teaching of Appellants, would not accept the full scope of the appealed claims as defining an effective method for preventing atherosclerosis.

Accordingly, in view of the wealth of guidance and example in the specification to support the scope of the claims, and in view of the dearth of evidence offered by the Examiner to undermine it, Appellants respectfully request that the rejection for lack of enablement under 35 U.S.C. §112, first paragraph, be reversed by the Board.

III. Appellants' Demonstration of Their Full Possession of the Invention at the Time of Filing Their Application

In the final Office Action, page 5, the Examiner maintained the rejection of Claims 28, 29 and 37-39 under 35 U.S.C. §112, first paragraph, for the reason that the specification is deemed not to reasonably convey to the person skilled in the art that the inventors were in possession of the claimed invention at the time of filing.

According to the Examiner,

> "In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention vaccine peptide comprising a universal helper T cell epitope portion linked to *any* B cell epitope portion of CETP and it's function production of native antibodies that recognize the subject's own, endogenous CETP, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed method for preventing atherosclerosis comprising administrating vaccine peptide, wherein vaccine peptide comprising a universal helper T cell epitope portion linked to *any* B cell epitope portion of CETP which retain the features essential to the instant invention." (*See*, final Office Action, page 6.) (emphasis in original).

The Examiner further directed Appellants to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, as published in the Federal Register, Vol. 66, No. 4, Jan. 5, 2001, pp. 1099-1111 (hereinafter "Guidelines"). (*See*, final Office Action, page 6.)

According to those Guidelines, the analysis of possession of the invention is akin to proving complete conception of an invention in an interference:

> "However, it is acknowledged that if evidence typically provided to prove a complete conception is present in the specification as filed, it would be sufficient to show possession. The Federal Circuit has stated '[t]he conception analysis necessarily turns on the inventor's ability to describe his invention with particularity. Until he can do so, he cannot prove possession of the complete mental picture of the invention.' (citation omitted)" (Guidelines at pp. 1101-1102.)

In discussing the General Principles to be applied by Examiners regarding compliance with the written description requirement, the Guidelines state:

> "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as *words*, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including *description of an actual reduction to practice*, **or** by showing that the invention was 'ready for patenting' such as by the disclosure of drawings **or** *structural chemical formulas* that show that the invention was complete, **or** by describing *distinguishing identifying characteristics* sufficient to show that the applicant was in possession of the claimed invention." (endnotes omitted; italics, bold and underlining added) (Guidelines at p. 1104.)

In the present application, there is an actual reduction to practice of treatment and prevention of atherosclerosis using a vaccine peptide according to the description. The vaccine peptide is identified using a "structural chemical formula", namely, a complete amino acid sequence (SEQ ID NO:2). The use of the vaccine peptide of SEQ ID NO:2 to inhibit formation of atherosclerotic plaque in the aortas of mammalian subjects is described in detail in Examples 6-10 of the specification (pages 32-38). Thus, the specification contains a demonstration of possession of the invention using the primary indicator called for by the Guidelines, namely, "description of an actual reduction to practice."

For any embodiment of the present claims not specifically exemplified in the specification, Applicants have provided a description of "distinguishing identifying characteristics" of the invention, for example, by providing: a complete description of the universal T cell epitope portion of the vaccine peptide; a complete description of the B cell epitope portion of the vaccine polypeptide; a description of methods and materials for linking the two portions; the complete amino acid structures for human and rabbit CETP (SEQ ID NOs:4 and 6); and descriptions of methods for assaying the effectiveness of the vaccine to cause production of endogenous CETP-binding antibodies, to cause increase in HDL-cholesterol levels and/or decrease in free cholesterol or LDL-cholesterol/VLDL-cholesterol levels, and to cause reduction in the formation of atherosclerotic plaque on arterial surfaces. Accordingly, all of the recitations of the claims under examination have been described with such particularity that a person skilled in the art would understand that the inventors were in possession of a full conception of every feature of the invention recited in the claims.

Clearly, the invention as defined in the present claims is supported by sufficient written description in the specification, if the claims are analyzed in accordance with the Guidelines cited by the Examiner.

The Examiner appears to require a written description of the use of every possible embodiment of the vaccine peptide to treat atherosclerosis in order to satisfy the written description requirement under 35 U.S.C. §112, paragraph 1. A moment's reflection will satisfy the Board that this is an impossible requirement that is neither demanded by 35 U.S.C. §112, first paragraph, nor imposed by an analysis of the application conducted under the Guidelines.

Also, in setting forth the rejection under 35 U.S.C. §112, first paragraph, the Examiner has misinterpreted the metes and bounds of the B cell epitopes of the present invention,

> "A description of a genus of polypeptide sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus,

> which features constitute a substantial portion of the genus." (See, final Office Action, page 7).

First, the B cell epitope "genus" of the present application is defined partly by structure (i.e., it must be part of the sequence of a full-length CETP), and partly by other properties (i.e., it must be a B cell epitope and, when linked with a universal helper T cell epitope, it must be antigenic). Contrary to the Examiner's assertion, Appellants have provided "a recitation of structural features common to the genus" i.e., B cell epitopes, and have taught "which features constitute a substantial portion of the genus", i.e., they all must elicit the production of autoantibodies to endogenous CETP when linked with the T cell epitope portion according to the claims.

What's more, the Examiner has cited no authority establishing a "minimum" recitation for a representative number of polypeptide sequences or a reason why Appellants have not provided a "representative" number of B cell epitopes capable of illustrating the entire genus for the understanding of those skilled in this art. There has been no evidence introduced into this record to contradict Appellants' position that a person skilled in this art knows what a CETP B cell epitope is and how to select one, especially in view of the guidance given in the present specification.

Accordingly, for the reasons set forth above, it is respectfully submitted that the present specification provides a written description sufficient to apprise a person skilled in the art that Applicants were in full possession of their invention as of the filing date. Consequently, the written description requirement of 35 U.S.C. §112, first paragraph, has been satisfied, and the rejection based on that requirement is in error and should be reversed by the Board.

IV. A. <u>The References Relied on by the Examiner are Improperly Combined</u>

The legal standard for rejecting claims as obvious over a combination of references was recently reviewed by the Court of Appeals for the Federal Circuit in *In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). As the court in *Kotzab* noted:

> "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of

> ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one 'to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.' *Id.* (quoting *W.L. Gore & Assocs. Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed.Cir.1983)).
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> "Most if not all inventions arise from a combination of old elements. *See In re Rouffett*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed.Cir.1998). Thus, every element of a claimed invention may often be found in the prior art. See *Id.* However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. See *Id.* Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *See In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed.Cir.1998): *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed.Cir.1984). . . .
>
> "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. In addition, the teaching, motivation or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. *See WMS Gaming, Inc. v. International Game Tech.*, 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). . . . Whether the Board relies on an express or an implicit showing, it must provide particular findings related thereto. *See Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617." (*In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000) (emphasis added)).

As noted above, the motivation to combine may derive from many sources, however, the range of possible sources that may serve as evidence for a motivation to combine references "does not diminish the requirement for actual evidence. That is, the

showing [of a motivation to combine] must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617, 1999 WL 246572 (Fed. Cir. 1999) (emphasis added). Furthermore, "[b]road conclusory statements standing alone are not 'evidence.'" *Id.*

The concept of attempting to actively immunize a mammal against its own, endogenous CETP is nowhere found in the prior art. That concept is found only in Appellants' specification. Nowhere in this record has the Examiner ever presented the required evidence FROM THE PRIOR ART of a motivation to control CETP activity by active immunization. The only references discussing immunization against a "self" protein, i.e., Stevens and Talwar, do not relate at all to cardiovascular disease and do not mention CETP or atherosclerosis. Neither do they advocate extension of their teachings (relating to human chorionic gonadotropin and maintenance of pregnancy) to any other protein or physical condition. Only by reference to Appellants' disclosure can a link between active immunization and control of CETP activity be made; without reference to Appellants' disclosure, the Stevens and Talwar references do not have any applicability to the field of CETP activity and lipid metabolism AT ALL.

The Whitlock reference was cited for its disclosure relating to the increase in HDL and decrease in CETP activity in rabbits when they were administered pre-made anti-human CETP antibodies. (*See*, final Office Action issued April 22, 2003, page 9). This is passive immunization.

Appellants point out that the Whitlock reference reports the results of administering a murine anti-human CETP monoclonal antibody (TP1) to rabbits. No rabbit anti-CETP antibodies are generated *within* the rabbit, by vaccination with a hybrid peptide or any other agent. The reference does not relate to the subject of the present invention, namely, generation of an antibody response to a subject's *own* CETP by administration of a hybrid peptide according to the claims as a therapeutic agent for the treatment or prevention of atherosclerosis.

The Whitlock reference shows *in vivo* modulation of CETP activity using premade, exogenously produced murine antibodies, but it provides no suggestion approximating Appellants' invention or linking the Stevens, Swenson, and Valmori

references together. The combination, as a whole, does not encourage a person of ordinary skill in the art to do what Appellants did, that is, to investigate whether injection of a hybrid peptide of particular construction into a subject could prompt the subject's immune system to recognize its own CETP as a foreign (non-self) protein and to inhibit its activity *in vivo* and that such a regimen would be useful for the treatment or prevention of atherosclerosis.

Again, nowhere in the final Office Action has the Examiner presented the required evidence of a motivation to combine the cited references to suggest methods for treating or preventing atherosclerosis by active immunization.

For example, with respect to Swenson, the Examiner states,

> "Swenson . . . teaches the immunogenic peptide CETP contains a B cell epitope and that administration of this peptide into animals results in production of anti-CETP antibody . . . Swenson further teaches the criticality of the carboxyl terminal 26 amino acid sequences derived from CETP, for the elicitation of antibody which decrease the level of endogenous CETP activity." (*See*, final Office Action, page 9).

While Swenson may show the use of xenogeneic human CETP or CETP fragments to immunize mice and raise murine anti-human CETP antibodies for *in vitro* use (e.g., immunoblots, assays, purification protocols), there is no teaching of raising anti-mouse CETP antibodies in mice or anti-rabbit CETP antibodies in rabbits. In other words, the Examiner's observation of anti-CETP antibodies is not an observation of antibodies recognizing endogenous CETP (i.e., as required in the present claims). Immunization against a foreign CETP has been shown in the references; active immunization against a self CETP has not.

The Valmori reference relates to multimeric constructs containing multiple repeats of a circumsporozoite protein sequence, made into a tetramer or an octamer using the polylysyl Multiple Antigen Peptide system, and in some instances also including one or two T cell epitope sequences from tetanus toxoid.

The multimeric constructs of Valmori are tested as vaccines against two species of *Plasmodium*, to confer immunity against infection by these external parasites. The

circumsporozoite proteins used in the Valmori constructs are foreign antigens, not endogenous proteins. There is no discussion in Valmori of raising an antibody response against any native protein in the vaccinated subjects.

From no combination of these references is the desirability of CETP as an autoimmune target suggested, and even the presence of a reference (Stevens) that involves attempts to raise an antigen response to a self antigen does not contain anything to encourage the person of ordinary skill in the art to apply the Stevens disclosure respecting hormones to a completely different class of protein, i.e., a large, constitutively produced, circulating serum protein that plays a role in a complex metabolic cascade, that is, CETP.

The differences between the methods of the present invention and the methods of Stevens are too great to admit of any motivation bridging between them. However, some differences are summarized below:

		Appellants' Invention	Stevens
1.	area of endeavor	lipoprotein metabolism affecting atherosclerosis	reproductive endocrinology
2.	endogenous antigen target	CETP (476 amino acids in human)	hCG (236 amino acids)
3.	target's expression *in vivo*	constitutive	pulsatile (upregulated only under certain conditions)
4.	concentration of target in plasma	1.87 mg/L - 4.23 mg/L for CETP	< 400 ng/L for hCG
5.	effect of active vaccination	unknown prior to Appellants' work	infertility

In view of the foregoing, Appellants submit that there is no motivation provided by Stevens to the person of ordinary skill in the art to apply its teachings to CETP or to even attempt active vaccination outside the realm of hormone-mediated conditions.

Appellants emphasize that the very idea of devising an immunogen to cause the endogenous CETP of a subject to be recognized by its own antibodies, where it previously was not, is an idea that is utterly absent from the citations of record. Without this spark of motivation, i.e., to consider endogenous CETP as a target for endogenous immune regulation, there is no reason why the hypothetical person of ordinary skill in the art would combine the teachings of the prior art as the Examiner has done.

The Examiner has not shown where in the descriptions of these references there is a motivation or suggestion to be combined with each other to pursue active immunization of an individual to elicit production of autoantibodies that recognize the individual's endogenous CETP.

The references cited by the Examiner generally fall into two categories: CETP references and tetanus toxoid references. The CETP references (Whitlock, Swenson) mention CETP or using human CETP to induce an immune response to human CETP as a foreign antigen in another species (i.e., mice, rabbits). The tetanus toxoid references (Stevens, Valmori) mention the use of tetanus toxoid to boost immune response against foreign antigen (*Plasmodium*, Valmori) or against self antigen (hCG, Stevens).

Although immune response to human CETP as a foreign antigen is described in the CETP references, there is no mention of even the concept of actively immunizing a subject so as to cause its immune system to react against its own CETP. And the tetanus toxoid references do not mention CETP or cardiovascular disease at all. Accordingly, Appellants submit that a bridge between the references does not exist outside Appellants' own specification, and the Examiner cannot point to any evidence in the art prior to Appellants' invention that raises even the concept, let alone the expectation, of positive results, i.e., that native CETP activity within an individual might be modulated by actively causing production *in vivo* of CETP-recognizing endogenous antibodies.

The foregoing arguments provide reasons why the person of ordinary skill in the art would NOT be motivated to combine the teachings of Whitlock or Stevens with those

of the other citations. In contrast, the Office Action contains no reasons why such a backward motivation would occur.

Appellants respectfully submit that the Examiner has fallen into the trap of hindsight reconstruction by mentally presuming the existence of a motivation or suggestion to combine all references to render Appellants' claimed methods obvious. The Examiner's motivation to combine references is only found in Appellants' own disclosure, which the patent law specifically forbids from being used against Appellants. After reading Appellants' disclosure and working examples, it may seem to the Examiner that others should have earlier conceived of the idea of administering conjugate peptides to produce an anti-atherogenic lipoprotein profile in order to treat or prevent development of atherosclerotic lesions. However, no such teaching or suggestion is found in the citations, alone or in combination, and the Examiner's reasoning rests only on the conclusory statements that motivation exists to tie the references together. Appellants submit that the Examiner has failed to provide particular evidence for the specific understanding or principles within the knowledge of a person of ordinary skill in the art that would have motivated the person without the benefit of Appellants' disclosure to combine the references cited by the Examiner and to arrive at Appellants' claimed methods. *See*, *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

From the foregoing it is readily seen that the Whitlock, Swenson, Stevens and Valmori references are improperly combined and should not be considered together in assessing the patentability of appealed Claims 28, 29, and 37-39. The addition of Stanton and Talwar in the rejection of Claim 39 does not provide any motivation to cure the failure of the primary and secondary references, as both Stanton and Talwar are silent on CETP and cardiovascular disease, falling into the same deficient category as Stevens and Valmori.

Appellants respectfully submit that without identifying with particularity the necessary *evidence* to support a motivation to combine the references as required by law, the combinations of the references of record are improper, and the rejection of Claims 28, 29, 37, and 38 should be reversed.

IV. B. No Combination of Any of the Examiner's Citations Shows or Suggests Successful Treatment or Prevention of Atherosclerosis

Even if the teachings of the references are combined, the combined teachings fail to provide a method for treatment or prevention of atherosclerosis. As pointed out above, the Stevens, Valmori, Stanton and Talwar citations make no mention of CETP or atherosclerosis. Of the references that at least pertain to CETP, neither Swenson nor Whitlock provides any demonstration of affecting the progression of atherosclerosis.

Swenson demonstrates the immunogenicity of human CETP *in mice* but provides no data, nor even discussion or speculation, regarding *in vivo* regulation of CETP activity. Manifestly, the reference falls far short of demonstrating any effect of altered CETP activity on atherosclerosis.

The Whitlock reference describes a short term passive immunization study of CETP activity wherein a murine monoclonal antibody reactive with human CETP is administered to rabbits to study *in vivo* inhibition of CETP activity. Administration of the anti-huCETP antibody was shown to inhibit CETP activity in rabbits by about 70% immediately after infusion, which inhibition fell to about 44% after 48 hours (*see*, e.g., Fig. 2, p. 131 of Whitlock). No data are provided showing that this short-term alteration of CETP activity has any effect on the development of atherosclerosis in the passively immunized rabbits. Appellants submit that, to the contrary, a person of ordinary skill in the art would observe the Whitlock data and conclude that a temporary reduction in CETP activity would have no effect on atherosclerosis, and indeed would have no lasting effect on CETP activity: The inhibition of CETP activity by passive immunization would fall off within a few days, after which CETP activity and cholesterol metabolism in the subject would be the same as before the passive immunization experiment.

Clearly, a person of ordinary skill in the art considering together the teachings of Whitlock, Swenson, Stevens, Valmori, Talwar, and Stanton ***has no basis*** to draw any conclusions with respect to the effect of inhibiting CETP on the progression of atherosclerosis. The Examiner in the final Office Action refers to the "fact" set forth at page 2 of Appellants' specification that decreased susceptibility to cardiovascular disease can be correlated with high circulating HDL levels, but this "fact" does not make the data

of Whitlock and Swenson more adequate for suggesting a treatment for atherosclerosis than it was before. The fact remains that nothing from the cited prior art illustrates a method by which the development of atherosclerosis can be checked.

In sharp contrast to the lack of information in the prior art, Appellants' disclosure contains working examples of administration of a vaccine peptide that results in production of antibodies reactive with endogenous CETP and that *furthermore* leads to a reduction in the formation of atherosclerotic lesions in the vaccinated subjects. Appellants' data, and not any data combined from the references, provides a basis for claiming the discovery of a method for treating or preventing atherosclerosis.

For the foregoing reasons, the combination of Whitlock, "the fact", Stevens, Swenson and Valmori does not provide a *prima facie* case of obviousness with regard to the methods of Claims 28, 29, 37 and 38; and the combination of Whitlock, "the fact", Stevens, Swenson and Valmori, further in view of Talwar or Stanton does not provide a *prima facie* case of obviousness with regard to the method of Claim 39. Accordingly, it is requested that those rejections be reversed by the Board.

IV. C. The Evidence of Record Shows the Lack of a Reasonable Expectation of Success in Active Immunization Against Self Proteins

Even if the teachings of the references cited by the Examiner are combined, the combinations still fail to establish obviousness of Appellants' invention, because the combinations fail to provide a person of ordinary skill in the art with a reasonable likelihood of success for treating or preventing atherosclerosis. This requirement for prior art references used to reject claims for obviousness is well established:

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under §103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) *whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. In re Dow Chemical Co.*, 837 F.2d 469, 473, 5

> U.S.P.Q.2d 1529, 1531 (Fed.Cir.1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*" *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) (emphasis added).

In the present case, no teaching of the prior art permits speculation as to how successful active immunization against endogenous CETP will be in combatting atherosclerosis.

The Examiner attempts to use Stevens as a general predictor of success for attempts to bypass the immune tolerance of individuals, stating,

> "Stevens teaches that active administration of antigen-tetanus toxoid conjugates to induce antibody responses for therapeutic effects are advantageous over passive administration of the antibody to the antigen because passive immunization procedures cause anti-antibody responses that cause serious side effect reaction upon repeated injection of the antibody." (*See*, final Office Action, page 10).

Stevens describes vaccine compositions for producing autoantibodies in an individual to inhibit the effect of an intermittently produced hormone. However, no protein mentioned in Stevens has a role in cholesterol metabolism or cardiovascular health. Thus, Appellants submit that a person of ordinary skill in the art would receive no guidance from Stevens that would be considered relevant or applicable to inhibiting CETP activity or treatment of atherosclerosis.

The Examiner also relies on the study in Whitlock as evidence that a person of ordinary skill in the art would have reasonably expected that Appellants' claimed methods would be effective at altering lipoprotein profiles or decreasing atherosclerotic lesions.

According to the Examiner,

> "Whitlock teaches that *in vivo* administration of CETP neutralizing antibodies leads to an elevation of circulating HDL, elevation in the ratio of circulating HDL to LDL, VLDL and total cholesterol, a decrease in the level of endogenous CETP activity and increase in the level of circulating HDL. Whitlock further teach that increase of HDL while decrease of VLDL would lead to decreased of

> LDL levels which would be beneficial for decrease in the development of atherosclerosis legions." (*See*, final Office Action, page 9).

However, injecting exogenously pre-made antibodies into a subject to obtain a beneficial effect is termed passive immunization, as exemplified by the traditional use of exogenously produced antiserum to counteract the effect of snake venom. In contrast, Appellants' claimed methods are methods to produce an active immunity inside an individual, i.e., wherein antigenic vaccine peptides are administered to the individual that are effective at eliciting *endogenous* production of autoantibodies that react with *endogenous* CETP. No immunologist, least of all the legal standard person of ordinary skill in the art, would equate passive immunization with active immunization; and no immunologist would confuse the immunogenicity of a foreign antigen with overcoming immune tolerance of endogenous, self proteins.

The Examiner evidently asserts that combining Whitlock's study using passive immunization with references such as Stevens makes Appellants' methods that employ active immunization against CETP predictable and, moreover, likely to succeed. However, the fact is that a person of ordinary skill in the art is well aware that passive immunization is NOT a reasonable predictor of active immunization, and *vice versa*.

This lack of predictability between passive immunity and active immunity in an individual is vividly illustrated in Michel et al., *Am. Heart J.*, *117*: 756-767 (1989), already of record (hereinafter, "Michel"). Michel is a published review of over 30 years of immunologic-based biochemical studies of the renin-angiotensin system (RAS). RAS is a system of at least four distinct proteins (i.e., renin, angiotensinogen, angiotensin-converting enzyme, and angiotensin II) involved in maintaining proper blood pressure. Michel describes how various investigators have attempted over the years to employ antibodies, both exogenously supplied (passive immunity) and endogenously produced (active immunity), as biochemical agents capable of controlling or altering aspects of internal blood pressure regulation. The results obtained in the studies on RAS vary widely and, taken together, illustrate that:

1. the use of passive immunization is not predictive of successful active immunization against a particular protein,

and

2. immunization experiments pertaining to one protein have virtually no value in predicting success of immunization against a different protein.

The examples in Michel demonstrate the above points:

For example, Michel et al. found only one biochemical study on the *in vivo* effects of passive transfer of rabbit antibodies against rat angiotensinogen which suggested angiotensinogen was involved in maintaining blood pressure. However, Michel et al. found no reports of successful active immunization against angiotensinogen using homologous (endogenous) angiotensinogenin in any species in nearly a decade since the study using passive immunity. (*See*, left column, p. 757 of Michel.)

In the case of angiotensin-converting enzyme, passive transfer of anti-converting enzyme antibodies could block pressor effect of angiotensins in rats, although immunoallergic responses to the foreign antibodies could quickly lead to death in rabbits. In attempts to actively immunize rats against converting enzyme, only one in 50 animals developed a high specific antibody titer capable of controlling the activity of the endogenous converting enzyme, but that animal died shortly after it was identified. (*See*, right column, p. 757 of Michel.)

In the case of angiotensins, some studies using passive transfer of antibodies against angiotensin II showed no effect on blood pressure, while others showed at least a transient result. However, in studies that attempted active immunization against endogenous angiotensin II, only one study in nine showed any effect in controlling blood pressure, *even though all reports showed endogenous production of antibodies to angiotensins*. Michel et al. opined that such results may indicate that the endogenously produced antibodies lacked sufficient affinity to affect the endogenous angiotensin II. (*See*, p. 758 of Michel).

In the case of renin, Michel reviewed *in vivo* studies on renin as far back as the 1950's. Studies using passive transfer of anti-renin antibodies yielded variable results depending on the laboratory, suggesting that some exogenously produced anti-renin antibodies were not effective in binding endogenously produced renin. The studies using active immunization against renin were also variable. Michel et al.'s own studies using an animal model indicated that all actively immunized animals developed autoimmune disease (*see*, p. 763 of Michel).

Appellants respectfully submit that Michel illustrates how variable results have been in attempts to effectively overcome the tolerance of an individual for a particular self protein in order to elicit production of autoantibodies that effectively bind or inhibit the particular endogenously produced protein target. In addition, Michel demonstrates how the results of studies using passive immunity against a protein are not capable of providing the person of ordinary skill in the art with any reasonable basis for predicting the outcome of an attempt to actively immunize an individual against the same protein. Thus, *in the absence of the teachings of Appellants' disclosure*, the Whitlock study using passive immunity would also have been considered by a person of ordinary skill in the art as lacking a reasonable expectation or likelihood of success for methods using active immunization to inhibit CETP and produce a beneficial effect. Accordingly, the passive immunity of the study of the Whitlock reference does not provide a reasonable expectation of success for Appellants' claimed methods that rely on active immunization.

Additionally, the studies reviewed in Michel demonstrate how immunization experiments pertaining to one protein (e.g., angiotensin) cannot be used as a reasonable indication of what to expect regarding immunization for a different protein (e.g., renin). Thus, references such as Stevens that describe results in active immunization of different hormones not only fail as reasonable predictors of success for one another, but also fail to provide any reasonable expectation of success in carrying out of methods which involve active immunization against a very different sort of protein (i.e., an abundant lipid transfer protein, as opposed to an intermittently produced hormone).

The Examiner is obliged to view the teachings of the prior art in the same way as a person of ordinary skill in the art at the time of Appellants' invention. Whatever else

might be determined herein of the level of skill in the art relevant to Appellants' invention, the person of ordinary skill is at least a scientist. Appellants respectfully submit that no scientist could possibly view the results of Stevens and the results reported by Michel (which show immunogenicity differences between protein targets as well as variability between passive vs. active immunization), and then conclude that the success of administering a vaccine peptide to an individual to elicit an antibody response capable of modulating the activity of CETP was in any way reasonably to be expected. A scientist would be obliged by the evidence in the prior art to conclude that no expectation could be formed in advance of the actual experiment to find out if active immunization were possible.

There is more evidence from the prior art on this record to conclude that active immunization will fail than there is evidence that it will succeed. Given the state of the art of immunology at the time of the invention, therefore, a person of ordinary skill in the art would never ignore variable data to blindly predict success in an untried field. In this case, Appellants were the first to perform an active immunization experiment, were the first to demonstrate control of CETP activity by endogenously produced anti-CETP antibodies, were the first to demonstrate that administration of an a CETP B cell epitope/universal helper T cell epitope conjugate would be effective in treating and preventing atherosclerosis, and were the first to be able to claim invention of the methods set forth in the pending claims.

Accordingly, for the reasons set forth above, the combinations of references proposed by the Examiner do not contain sufficient basis for reasonably predicting success in treating or preventing atherosclerosis. Moreover, when considered in the light of additional background art such as Michel, the expectation of success diminishes significantly. Therefore, Appellants respectfully submit that the Examiner has failed to establish that the methods of Claims 28, 29, and 37-39 are obvious from the prior art, and the final rejections of those claims under 35 U.S.C. §103 should be reversed.

IV. D. With Respect to Treatment and Prevention of Atherosclerosis by Active Immunization, Appellants' Results Are Unexpected and Therefore Indicative of Non-Obviousness

Even if the references are combined as proposed by the Examiner, the person of ordinary skill in this art could not have expected the results reported by Appellants' claimed methods as demonstrated by the various examples in the specification.

Without the benefit of Appellants' disclosure, it is difficult to believe that a person of ordinary skill in this art would ever expect to design the elected species of conjugate peptide and then successfully carry out the methods for treating or preventing atherosclerosis as outlined in Claims 28, 29, and 37-39. Following the Examiner's reasoning, the person of ordinary skill in the art would read the cited references and, thereby, be so equipped and enabled, without inventive effort, to design a peptide immunogen including the elected species; to expect such a peptide immunogen would be adequately soluble or dispersible for administration to an individual; to expect that such a peptide immunogen would properly display a helper T cell epitope and a B cell epitope to the immune system in the individual; to expect such a peptide immunogen would be sufficiently stable *in vivo* to elicit an immune response without requiring further modification; to expect that any antibody produced in such an immune response would not only recognize the peptide immunogen but would also bind the individual's native, endogenously produced, circulating CETP; to expect that the antibody response would be sustained and not immediately cleared without significant effect on CETP; to expect that such a sustained immune response would only affect CETP activity without destruction of tissues and organs; to expect that such an immune response would produce sufficient levels of antibody that would effectively modulate the activity of the relatively high circulating levels of endogenous CETP as opposed to the transient, low levels of hormone targets described in Stevens; to expect that such an immune response would continue to modulate endogenous CETP without diminishing in 48 hours as in Whitlock; and to expect that such an immune response to endogenous CETP would alter lipoprotein levels and would prevent development of atherosclerotic lesions to the immense benefit of the vaccinated individual.

Appellants submit that this string of expectations which the Examiner ascribes to a person of ordinary skill in the art working without data or an actual example of a vaccine peptide according to the present invention not only outstrips the expectations of the Appellants themselves prior to their inventive work but makes the person of ordinary skill in the art, in this case, the most prescient scientist of all time. But even presuming this level of expectation, i.e., that none of the myriad factors alluded to above would turn out to defeat the hypothetical treatment and that only the best results of all the references would be realized when transferred to the field of Appellants' invention, the results predicted by the combined citations would still only lead to the expectation of a transient reduction of CETP activity (e.g., a reduction of only a matter of hours as in Whitlock), which transient reduction would be overcome by clearance of the antibodies or possibly neutralized by upregulation of CETP production *in vivo*.

Appellants' results show, by contrast, that the actual performance of this work produced an antibody response that was specific (Example 6, discussed *infra.*) and which produced lasting effects on cholesterol and HDL levels in vaccinated individuals (Figs. 11 and 12).

Moreover, there is no way for a person of ordinary skill in the art to form an expectation as to the results of vaccination on the extent of development of atherosclerotic lesions, because none of the references includes any teachings that link reduction of CETP activity in plasma with actual reduction in arterial plaque. Thus, Appellants' Example 10 and Fig. 13, which show the effect of their observed degree of modulation of endogenous CETP activity on the prevention of atherosclerotic lesions, present results that are clearly unexpected and unpredictable on the basis of the prior art.

In addition, the *magnitude* of the effect of Appellants' treatment on the size of aortic lesions could not have been predicted from the citations of record: Fig. 13 of Appellants' application demonstrates that the administration of a vaccine peptide in accordance with Appellants' methods led to more than 50% lower size of atherosclerotic lesions. In contrast, considering all of the data of the Whitlock reference, "the fact" on page 2 of Appellants' specification, the Stevens reference, the Swenson reference, the Valmori reference, the Stanton reference, and the Talwar reference -- considering all

those teachings together but without the benefit of Appellants' data -- no expectation as to the amount of plaque reduction can be made. This is because there are no data in the prior art allowing even speculation on how much of an effect, if any, reduction of CETP activity would have on development of atherosclerotic plaque.

In view of this, any demonstrated reduction in plaque formation would be an unexpected result, but certainly over 50% less plaque attributable to the treatment of the invention could not have been imagined. Such unexpected results, wholly unimaginable to the person of ordinary skill in the art at the time of Appellants' invention, directly indicate the non-obviousness of Appellants' Claims 28, 29 and 37-39.

For the foregoing reasons, Appellants' invention as recited in the claims on appeal is unobvious in view of the citations of record, and the final rejection of those claims should be reversed by this Board.

V. Examiner's Reasoning in the Final Office Action is Incorrect and Unsupported by the Cited Case Law

For reasons discussed in detail above, the appealed claims are not obvious over the cited prior art within the meaning of 35 U.S.C. §103. Moreover, the reasoning of the Examiner in maintaining the rejections and the case law relied on by the Examiner for support are both incorrect.

With respect to Appellants' assertion in previous responses that the Examiner has used Appellants' disclosure to tie the references together, i.e., has employed hindsight reasoning to support the obviousness rejection, the Examiner states,

> "In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971)." (See, final Office Action, page 8).

The *McLaughlin* decision can be distinguished from the present case on its facts. In *In re McLaughlin*, the CCPA upheld an examiner's rejection under 35 U.S.C. §103 based on the combination of one primary reference (Cook) in view of three secondary references (Robertson, Aquino, and Lundvall).

While McLaughlin argued that the references were improperly combined, he only distinguished the primary reference, without accounting for the relevant teachings of the secondary references. According to the Court:

> "[McLaughlin] argues that, while the reference does show elongated, longitudinally offset doors, it does not suggest such an arrangement in combination with a bulkhead and side fillers because of the patentee's expressed desire to have a car capable of being loaded and unloaded simultaneously from both sides, which is not the desire of appellant, nor even possible, he urges, with his arrangement." (443 F.2d at 1395, emphasis added).

In rejecting McLaughlin's argument the Court stated,

> "[T]he test for combining references is not what the individual references themselves suggest but rather what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art" (443 F.2d at 1395).

In upholding the Board's decision with respect to some claims, the Court concluded that while the Cook reference relating to a railroad car capable of receiving palletized loads did not refer to panels and bulkheads for securing the loads, the secondary references, which all related to securing loads in railroad cars, supplied the missing elements:

> "The Cook patent does indicate that the car shown therein is suitable for carrying palletized loads . . . Since the secondary references show that it was well known to use side filler panels and bulkheads to confine palletized loads to prevent lateral and longitudinal shifting, we agree that those references would have suggested use of such panels and bulkheads with the Cook car for the same purpose." (443 F.2d at 1395)

Therefore, the Court in *McLaughlin* pointed out that all references related to various schemes of loading railway cars, and it was not effective for McLaughlin to argue against the combination of references by distinguishing only the primary reference and ignoring the relevant teachings of the secondary references.

In contrast to the facts in *McLaughlin*, Appellants have continually demonstrated in the present application that the references cited by the Examiner have no such common technological thread running through them. The technology of loading freight cars was common to all the references in *McLaughlin* AND was the field of McLaughlin's invention. In the present case, as discussed in detail above, the primary reference (Whitlock) relates to passive immunization with CETP, but the secondary references relate to hormones (Stevens, Talwar) or parasites (e.g., *Plasmodia*, Valmori), and none of the references relates to active immunization against endogenous CETP.

Moreover, Appellants have not merely addressed one reference and ignored the rest, as was the case in *In re McLaughlin*. Appellants have carefully reviewed the teachings of every reference herein and have discussed their combined teachings, even though they assert that such disparate teachings cannot be properly or even logically combined.

Also, in the final Office Action, with respect to Appellants' previous explanations as to the distinctions between the teachings of the cited references and the present application, the Examiner states,

> "Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC 103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see *In re Keller*, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981)" (See, final Office Action, page 8).

The Examiner has cited *In re Keller*, 642 F.2d 413, 208 U.S.P.Q. 871 (CCPA 1981) for the assertion that Appellants have, in the past, improperly attacked each reference individually as opposed to whether the combination of references would

suggest Appellants' invention to one skilled in the art. However, upon review of Appellants' previous responses, it is clear that the references have not been attacked individually, but rather, each reference has been discussed individually to demonstrate the disparity in their fields of endeavor and then to demonstrate that their combination would never lead one of ordinary skill in the art to Appellants' invention.

In *In re Keller*, the CCPA upheld the Board's rejection of Appellant's invention under 35 U.S.C. §103 based on two references (Keller and Berkovits) in view of one secondary reference (Walsh). The Court upheld the Patent Office's decision to reject Keller's claims because Keller admitted the primary references were related to the disclosed invention:

> "Appellant admitted below that 'both [primary references] disclose cardiac pacers. . .', and asserted that these patents 'represent conventional thinking with respect to cardiac pacing at the time the present invention was made'" 642 F.2d at 424).

Keller attempted to rebut the rejection by distinguishing the secondary reference only as opposed to the combination of primary and secondary references:

> "As characterized by appellant, the Cywinski affidavit offered as objective evidence of non-obviousness 'concerns itself mainly with the question of whether the [secondary reference] suggest [sic] the use of digital timing in a cardiac pacer . . . '. But one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references." 642 F.2d 426, 208 U.S.P.Q. --, *citing*, *In re Young*, 403 F.2d 754, 159 U.S.P.Q. 725 (CCPA 1968).

In contrast to *In re Keller*, Appellants have not attempted to rebut the §103 rejections by attacking one secondary reference only, in the hope that it would also negate all the other references, but rather, Appellants have properly addressed the teaching of each reference individually to demonstrate that the teachings of each reference combined would not suggest Appellants' invention to one skilled in the art.

As further support for the §103 rejection, the Examiner states,

> "Moreover, it is noted that at the time the invention was made active immunization against 'self-antigens' that is

> breaking of tolerance to endogenous proteins by enhancing the immunogenicity of 'self-antigen' with universal helper T cell epitope was well known in the art. Thus it would be obvious to one of ordinary skill in the art at the time the invention was made to use active immunization using self CETP. *The rationale to support a rejection under 35 U.S.C. 103 may rely on logic and sound scientific principle. In re Soli*, 317 F.2d 941, 137 USPQ 797 (CCPA 1963)." (See, final Office Action, page 8). (emphasis added).

Again, the Examiner has misapplied the standard set forth in the case law, to rationalize the unwarranted combination of unrelated references.

In *In re Soli*, the application claimed a method for determining the location of subterranean hydrocarbon deposits (i.e., oil) by analyzing soil samples for the presence of hydrocarbon-oxidizing bacteria in an area where a deposit was likely to be found. The method included the steps of collecting the soil, incubating samples separately in methane, propane, or air (control), and determining the presence/amount of hydrocarbon oxidizing bacteria by analyzing the level of turbidity of the cultures. The prior art references cited against Soli disclosed one or more of the claimed method steps in the relevant context of determining the level of hydrocarbon-oxidizing bacteria in soil.

In distinguishing the prior art cited by the examiner, Soli stated that no reference taught the control step of separately incubating a soil sample in air, (which would not support the growth of the indicator bacteria) and no reference disclosed the step of keeping the ratio of soil to culture medium in the growth chamber to a minimum.

In upholding the examiner's rejection, the Court stated, first with respect to the air incubation control step,

> "This is not a case where the examiner's allegation appears to be based on mere conjecture. On the contrary, this court takes judicial notice of the use of 'controls' in various experimental procedures . . . It is well within the ordinary skill of the art to use a control." (317 F.2d at 946)

and second, with respect to the soil to culture medium ratio step,

> "We are constrained to agree with the Examiner that this appears to be no more than conventional procedure in bacteriological experiments." (317 F.2d at 947)

Finally, as stated above, the Examiner's reference to this case in the final Office Action not only takes a quote out of context, but misapplies the standard for establishing a *prima facie* case of obviousness clearly set forth by the Court in *Soli*:

> "When, as in the instant case, the Patent Office finds, in the words of 35 U.S.C. 103, 'differences between the subject matter sought to be patented and the prior art, 'it may not, without some basis in *logic* or *scientific principle*, merely allege that such differences are either obvious or of no patentable significance and thereby force an appellant to prove conclusively that it is wrong. Such is not and never has been the rule relating to burden of proof in this court." 317 F.2d at 947, 137 U.S.P.Q at -- (*italics* show portion of quote cited by the Examiner in the final Office Action).

Therefore, unlike the present case, the Court in *In re Soli* supported the examiner's application of scientific common sense: Judicial notice was taken of the use of controls and other conventional scientific procedures. In the present case, the Examiner has merely cited *In re Soli* to escape from stating the logic or scientific principal that would lead a person of ordinary skill in the art to draw the conclusions the Examiner has.

For example, the Examiner concludes that "it would be obvious to one of ordinary skill in the art . . . to use active immunization using self CETP", because "at the time the invention was made active immunization against . . . endogenous proteins by enhancing the immunogenicity of 'self-antigen' with universal helper T cell epitope was well known in the art". But as demonstrated by Appellants in Section IV. C., active immunization against self proteins was NOT "well known" in the art -- the citations relied on by the Examiner as well as the Michel et al. reference of record demonstrate that active immunization against self is unpredictable, more often unsuccessful than successful, and incapable of generalization (i.e., successful active immunization against one self protein is not predictive of success against another protein).

Thus, the Examiner must *ignore* logic and *ignore* scientific principle to make the combinations and conclusions contained in the final Office Action, and *In re Soli* manifestly cannot be cited to support that.

CONCLUSION

Appellants respectfully submit that all rejections of the final Office Action should be reversed because:

- Issues of obviousness over the same references and of the suitability of the disclosure to fully describe and enable the claim terms have been previously resolved before the U.S. Patent Office in Appellants' favor during the prosecution of the predecessor cases to this case, namely, U.S. 6,410,022 (Tab B) and U.S. 6,555,113 (Tab C);
- The data presented in the present application directly support claims to a method of preventing atherosclerosis, and the ample discussion preceding the working examples permits the ready construction, administration and testing of the full range of antigenic vaccine peptides taught as useful according to the methods of the appealed claims;
- The detailed description of the invention and the working examples amply demonstrate that Appellants' were in full possession of their claimed methods at the time the application was filed;
- The two reference combinations relied on by the Examiner to maintain rejections under 35 U.S.C. §103 fail to establish the obviousness of any of Claims 28, 29, 37, 38 or 39 because:
    - There is no substantial evidence of a sufficient motivation or teaching *in the prior art* to combine the references relied on by the Examiner,
    - Even if the references are combined, there is no demonstration from either reference combination of an effect on atherosclerosis from active or passive immunization against any protein,
    - There is no substantial evidence from either combination of references that a person of ordinary skill in the art would have a reasonabe expectation of successfully treating or preventing atherosclerosis by a method of active immunization of an individual to produce antibodies recognizing the individual's endogenous CETP, and in fact there is substantial evidence of

record that a person of ordinary skill in the art would NOT have expected success in such a method, and

- The results reported for the first time in Appellants' application are unexpected with respect to any results predictable from a consideration of the prior art.

Accordingly, for the reasons set forth herein, the final rejections applied against appealed Claims 28, 29, and 37-39 under 35 U.S.C. §112, first paragraph, and under 35 U.S.C. §103(a) as set forth in the final Office Action of April 22, 2003 are in error and should be reversed by this Board.

Respectfully submitted,

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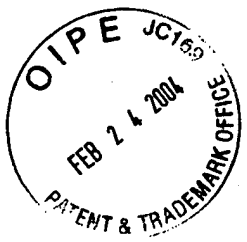


Appealed Claims

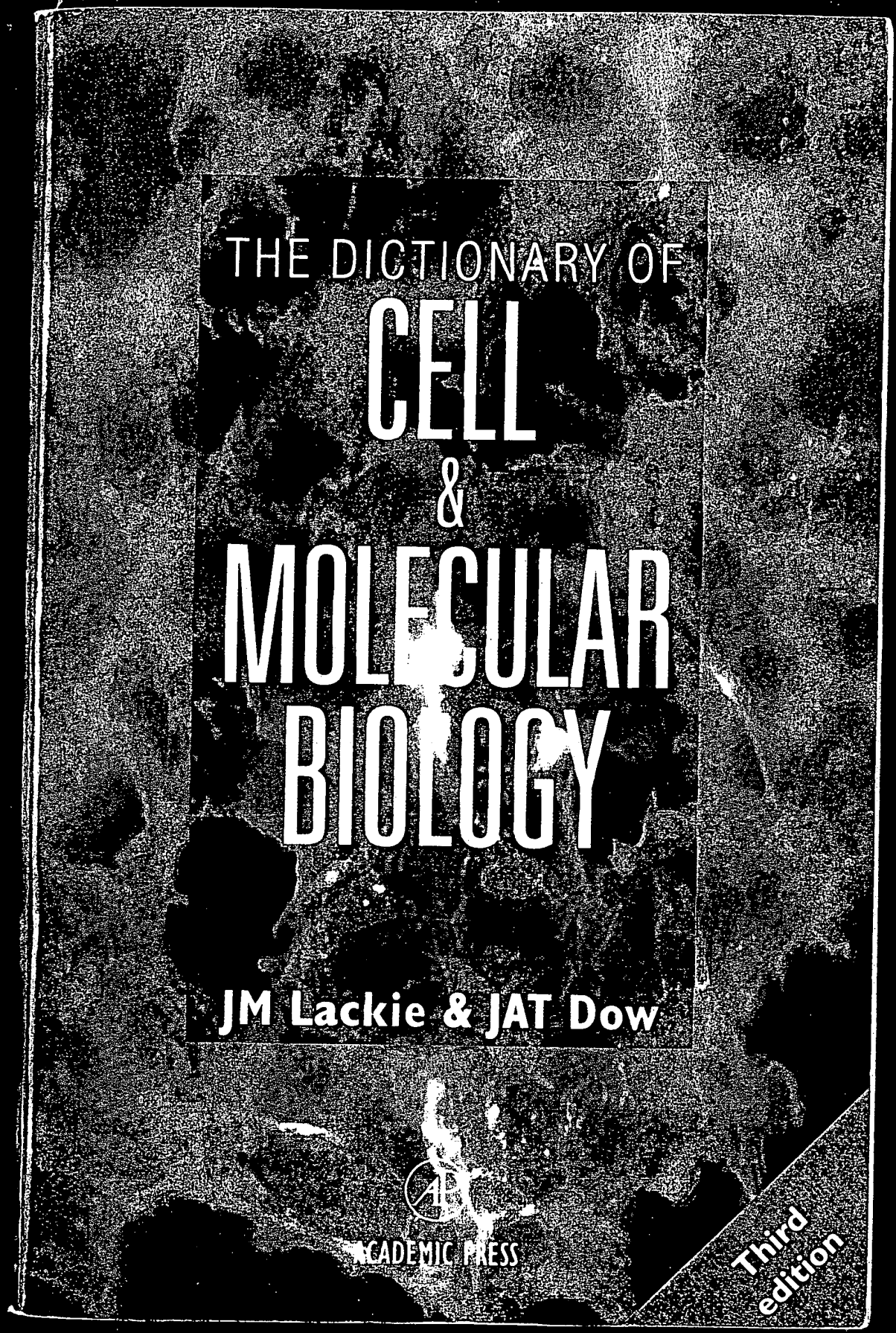
28. A method for treating or preventing atherosclerosis in a human or animal comprising administering to said human or animal an antigenic vaccine peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises a B cell epitope of CETP.

29. The method according to claim 28, wherein said helper T cell epitope portion comprises a helper T cell epitope derived from an antigenic peptide selected from the group consisting of tetanus toxoid, diphtheria toxoid, pertussis vaccine, Bacile Calmette-Guerin (BCG), polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, purified protein derivative of tuberculin, keyhole limpet hemocyanin, hsp70, and combinations thereof.

37. The method according to claim 28, wherein said B cell epitope portion of the antigenic vaccine peptide comprises 6 to 26 consecutive amino acids of the carboxyl terminal 26 amino acids of human cholesteryl ester transfer protein (SEQ ID NO:1).

38. The method according to claim 37, wherein the vaccine peptide comprises the amino acid sequence of SEQ ID NO:2.

39. The method according to claim 37, wherein the vaccine peptide comprises a dimer of the amino acid sequence of SEQ ID NO:2.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The Dictionary of CELL AND MOLECULAR BIOLOGY

Third Edition

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Co-staining of filamentous actin (red) and vinculin (green) in HEK 293 cells. Vinculin which is associated with focal contacts localizes to the ends of the actin cables. Acquired digitally with a Zeiss Axiovert 135 fluorescence microscope, a Hamamatsu CCD camera and OpenLab 2.0 (Improvision, Coventry, England).

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thyroiditis. The cubical cells line small ***acini*** and have ***eosinophilic*** granular cytoplasm and often bizarre nuclear morphology. Also known as Hurthle cells, oxyphil cells or oncocytes.

asn See ***asparagine***.

asp See ***aspartate***.

asparaginase Enzyme (EC 3.5.1.1) that hydrolyzes L-asparagine to L-aspartate and ammonia that is used as an anti-tumour agent especially against lymphosarcoma and lymphatic leukaemia.

asparagine (β-asparagine; Asn; N) The β-amide of aspartic acid (132 D); the L-form is one of the 20 amino acids directly coded in proteins. Coded independently of aspartic acid. See Table A2.

aspartame Trademark for Asp-Phe Methyl Ester, an artificial sweetener.

aspartate (aspartic acid; Asp; D) L-aspartate is one of the 20 amino acids directly coded in proteins (133D); the free amino acid is a neurotransmitter. See Table A2.

aspartic acid See ***aspartate***.

aspartokinase Enzyme that phosphorylates L-aspartate to produce aspartyl phosphate.

aspergillins Family of toxins (17 kD) produced by *Aspergillus*. All are ribonucleases and disrupt protein biosynthesis. Includes ***alpha-sarcin***, mitogillin, restrictocin and Asp fl.

aspergillosis Lung disease caused by fungi of the genus *Aspergillus*.

Aspergillus A genus of common ascomycete fungi found in soil. Industrially important in production of organic acids, and a popular fungus for genetic study (esp. *A. niger*).

aspirin (acetyl salicylate) An analgesic, antipyretic and antinflammatory drug. It is a potent ***cyclooxygenase*** inhibitor and blocks the formation of ***prostaglandins*** from ***arachidonic acid***.

association constant (K_a; K_{ass}) Reciprocal of ***dissociation constant***. A measure of the extent of a reversible association between two molecular species at equilibrium.

astacin Astacin, a zinc-endopeptidase from crayfish (*Astacus*), is the prototype for the astacin family of metallo-endopeptidases. Family includes ***BMP-1***, Meprin A, ***stromelysin*** 1, and ***thermolysin***.

aster Star-shaped cluster of microtubules radiating from the polar ***microtubule organizing centre*** at the start of mitosis.

asthma Inflammatory disease of the airways involving marked eosinophil infiltration and remodelling of the airways. Attacks can be triggered by allergic responses, physical exertion, inhaled chemicals or stress and involve wheezing, breathlessness and coughing.

astroblast An embryonic ***astrocyte***.

astrocyte A ***glial cell*** found in vertebrate brain, named for its characteristic star-like shape. Astrocytes lend both mechanical and metabolic support for neurons, regulating the environment in which they function. See ***oligodendrocytes***.

astrocytoma A neuro-ectodermal tumour (***glioma***) arising from ***astrocytes***. Probably the commonest glioma, it has a tendency to become ***anaplastic***.

astroglia See ***astrocytes***.

astrogliosis Hypertrophy of the ***astroglia***, usually in response to injury.

Astropectinidae Family of echinoderms that includes many starfish species with long spines.

astrotactin Neuronal surface glycoprotein (100–105 kD; three ***EGF-like*** repeat domains, two ***fibronectin*** III repeats), that functions in murine cerebellar granule cell migration ***in vitro***, acting as the ligand for neuron–glial cell binding. Message has been detected in neuronal precursors in the cerebellum, hippocampus, cerebrum and olfactory bulb in the ***brain***. See ***weaver*** mutant.

astroviruses Spherical viruses with 5- or 6-pointed star-shaped surface pattern. May be associated with enteritis in various vertebrates.

ataxia telangiectasia Louis Bar syndrome; a hereditary ***autosomal*** recessive disease in humans characterized by a high frequency of spontaneous chromosomal aberrations, neurological deterioration and susceptibility to various cancers. Ataxia: imbalance of muscle control; telangectasia: dilated capillary vessels. In part an immune deficiency disease and in part one of DNA repair; it is believed to be due to hypersensitivity to background ionizing radiation.

ATCase (aspartate transcarbamylase) Enzyme (EC 2.1.3.2) that catalyses the first step in pyrimidine biosynthesis, condensation of aspartate and carbamyl phosphate. Positively allosterically regulated by ATP and negatively by CTP; classic example of an allosterically regulated enzyme. Bacterial ATCases exist in three forms: class A (ca 450–500 kD), class B (ca 300 kD) and class C (ca 100 kD).

ATCC The American Type Culture Collection, repository of many eukaryotic cell lines (which may be purchased). Comparable collections of microorganisms, protozoa etc. are kept.

atheroma Degeneration of the walls of the arteries because of the deposition of fatty plaques in the ***intima*** of the vessel wall, and scarring and obstruction of the lumen.

atherosclerosis Condition caused by the deposition of lipid in the wall of arteries in (atheromatous plaques). Migration of smooth muscle cells from media to intima, smooth muscle cell proliferation, the formation of ***foam cells*** and extensive deposition of extracellular matrix all contribute to the formation of the lesions that may ultimately occlude the vessel or, following loss of the endothelium, trigger the formation of thrombi. Should be distinguished from ***arteriosclerosis*** which is a more general term usually applied to arterial hardening through other causes. Atherosclerosis is a major

medical problem in most of the developed world.

ATM Protein product of the gene mutated in ***ataxia telangiectasia*** (AT), a member of the phosphatidylinositol-3-kinase family. ATM constitutively binds to the SH3 domain of the tyrosine kinase c-***Abl*** in normal but not AT cells and ATM seems to activate DNA damage-induced activation of c-Abl (which is deficient in AT cells).

atomic force microscopy (AFM) A form of ***scanning probe microscopy***, in which a microscopic probe is mechanically tracked over a surface of interest in a series of *x*-*y* scans, and the force encountered at each coordinate measured with piezoelectric sensors. This provides information about the chemical nature of a surface at the atomic level.

atopy Allergic (***hypersensitive***) response at a site remote from the stimulus (eg. food-induced dermatitis).

ATP (adenosine 5′ triphosphate) Synthesis in cells from ADP is driven by energy-yielding processes. Enzymic transfer of the terminal phosphate or pyrophosphate to a wide variety of substrates provides a means of transferring chemical free energy from metabolic to catabolic processes.

ATPase An enzyme capable of releasing the terminal (γ) phosphate from ATP, yielding *ADP* and inorganic phosphate. The description could mislead, because in most cases the enzymic activity is not a straightforward hydrolysis, but is part of a coupled system for achieving an energy-requiring process, such as ion-pumping or the generation of motility.

ATP-binding site ('A' motif) A consensus domain found in a number of ATP- or GTP-binding proteins, for example ***ATP synthase, myosin heavy chain, helicases,*** thymidine kinase, ***G-protein*** α-subunits, GTP-binding ***elongation factors, Ras*** family. Consensus is: (A or G)-XXXXGK-(S or T); this is thought to form a flexible loop (the P-loop) between α-helical and ***beta-pleated sheet*** domains.

ATP synthase A proton-translocating ***ATPase***, found in the inner membrane of ***mitochondria, chloroplasts*** and the plasmalemma of ***bacteria***. It can be known as the F1/Fo or CF1/CFo ATPase, or as the class of F-type ATPases. In all these cases, the enzyme is driven in reverse by the large ***proton motive force*** generated by the ***electron transport chain***, and thus synthesizes, rather than uses, ***ATP***. See also ***chemiosmosis, V-type ATPase, P-type ATPase.***

atria (plural) See ***atrium***.

atrial natriuretic factor Obsolete name for ***atrial natriuretic peptide.***

atrial natriuretic peptide (ANP) A polypeptide hormone found mainly in the atrium of many species of vertebrates. It is released in response to atrial stretching, and thus to elevated blood pressure. ANP acts to reduce blood pressure through stimulating the rapid excretion of sodium and water in the kidneys (reducing blood volume), by relaxing vascular smooth muscle (causing vasodilation), and through actions on the brain and adrenal glands.

atrium (plural, atria) A cavity in the body, especially either of the two upper chambers of the heart in higher vertebrates.

atrophy Wasting away of tissue.

atropine An alkaloid, isolated from deadly nightshade, *Atropa belladonna*, that inhibits muscarinic acetylcholine receptors. Applied to the eye it causes dilation of the pupil that is said to enhance the beauty of a woman, hence belladonna as the specific name of the plant from which the ancients extracted the drug.

attachment constriction See ***centromere.***

attachment plaques Specialized structures at the ends of a chromosome by which it is attached to the nuclear envelope at ***leptotene*** stage of mitosis.

attacins Antibacterial proteins (20–22 kD) produced by insect haemocytes following bacterial challenge. May be basic or acidic.

attennuation Viruses that have been ***saged*** extensively may become a uated (non-virulent), and can be us a vaccine.

atx A, B & C See ***ammodytoxins.***

AUG The ***codon*** in ***messenger RNA*** specifies initiation of a polype chain, or within a chain, incorporati a ***methionine*** residue.

Aurelia aurita Common jellyfish: t parent disc with four blue/p horseshoe-shaped gonads clearly vi Phylum Cnidaria; class Scyphozoa.

aurosome Gold-containing secon lysosome found in patients treated gold complexes.

aurovertin Inhibitor of the ***respira chain*** that binds to ATPase.

Australia antigen An envelope ant now known as HBsAg of ***hepatit*** virus. Appearance of the antige serum is associated with a phase of infectivity.

autacoids Local hormones such as ***h mine, serotonin, angiotensin, eicosan***

autoantibody Antibody that reacts wit antigen that is a normal compone the body. Obviously this can lea some problems, and autoimmunity been proposed as a causative factor number of diseases such as rheuma arthritis. See also ***systemic lupus er ematosus, Hashimoto's thyroid myasthenia gravis.***

autocatalytic A compound that catalyse own chemical transformation. N commonly a reaction that is catalyse one of its products or an enzy catalysed reaction in which on the products functions as an enz activator.

autochthonous Found in the place whe was originally formed, indigenous.

autocrine Secretion of a substance, suc a ***growth factor***, that stimulates secretory cell itself. One route